UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/632,725	08/01/2003	David E. Wolf	205-007US2	2807

27791 7590 07/26/2007

ALLISON JOHNSON, P.A.
LAKE CALHOUN EXECUTIVE CENTER
3033 EXCELSIOR BLVD., SUITE 467
MINNEAPOLIS, MN 55416

EXAMINER	
SHIBUYA, MARK LANCE	
ART UNIT	**PAPER NUMBER**
1639	
MAIL DATE	**DELIVERY MODE**
07/26/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Advisory Action Before the Filing of an Appeal Brief	Application No. 10/632,725	Applicant(s) WOLF ET AL.	
	Examiner Mark L. Shibuya, Ph.D.	Art Unit 1639	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 26 June 2007 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☐ The period for reply expires _____months from the mailing date of the final rejection.
   b) ☒ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☒ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): 35 USC 112, 2d para rejection for lack of antecedent basis .
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: *None*.
   Claim(s) objected to: _____.
   Claim(s) rejected: *59-66 and 118-138*.
   Claim(s) withdrawn from consideration: *68*.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: Please see attached.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other: _____.

Mark L. Shibuya, Ph.D.
Primary Examiner
Art Unit: 1639

Notice of Non-Compliant Amendment (37 CFR 1.121)	Application No. 10/632,725	Applicant(s) WOLF ET AL.	
	Examiner Mark L. Shibuya, Ph.D.	Art Unit 1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

The amendment document filed on 6/26/2007 is considered non-compliant because it has failed to meet the requirements of 37 CFR 1.121 or 1.4. In order for the amendment document to be compliant, correction of the following item(s) is required.

THE FOLLOWING MARKED (X) ITEM(S) CAUSE THE AMENDMENT DOCUMENT TO BE NON-COMPLIANT:

- ☐ 1. Amendments to the specification:
  - ☐ A. Amended paragraph(s) do not include markings.
  - ☐ B. New paragraph(s) should not be underlined.
  - ☐ C. Other _____.
- ☐ 2. Abstract:
  - ☐ A. Not presented on a separate sheet. 37 CFR 1.72.
  - ☐ B. Other _____.
- ☐ 3. Amendments to the drawings:
  - ☐ A. The drawings are not properly identified in the top margin as "Replacement Sheet," "New Sheet," or "Annotated Sheet" as required by 37 CFR 1.121(d).
  - ☐ B. The practice of submitting proposed drawing correction has been eliminated. Replacement drawings showing amended figures, without markings, in compliance with 37 CFR 1.84 are required.
  - ☐ C. Other _____.
- ☒ 4. Amendments to the claims:
  - ☐ A. A complete listing of all of the claims is not present.
  - ☐ B. The listing of claims does not include the text of all pending claims (including withdrawn claims)
  - ☒ C. Each claim has not been provided with the proper status identifier, and as such, the individual status of each claim cannot be identified. Note: the status of every claim must be indicated after its claim number by using one of the following status identifiers: (Original), (Currently amended), (Canceled), (Previously presented), (New), (Not entered), (Withdrawn) and (Withdrawn-currently amended).
  - ☐ D. The claims of this amendment paper have not been presented in ascending numerical order.
  - ☒ E. Other: *Claim 68 should have the status identifier of "withdrawn".*.
- ☐ 5. Other (e.g., the amendment is unsigned or not signed in accordance with 37 CFR 1.4):

_____

For further explanation of the amendment format required by 37 CFR 1.121, see MPEP § 714.

TIME PERIODS FOR FILING A REPLY TO THIS NOTICE:

1. Applicant is given **no new time period** if the non-compliant amendment is an after-final amendment or an amendment filed after allowance. If applicant wishes to resubmit the non-compliant after-final amendment with corrections, the **entire corrected amendment** must be resubmitted.

2. Applicant is given **one month**, or thirty (30) days, whichever is longer, from the mail date of this notice to supply the correction, if the non-compliant amendment is one of the following: a preliminary amendment, a non-final amendment (including a submission for a request for continued examination (RCE) under 37 CFR 1.114), a supplemental amendment filed within a suspension period under 37 CFR 1.103(a) or (c), and an amendment filed in response to a *Quayle* action. If any of above boxes 1. to 4. are checked, the correction required is only the **corrected section** of the non-compliant amendment in compliance with 37 CFR 1.121.

   Extensions of time are available under 37 CFR 1.136(a) only if the non-compliant amendment is a non-final amendment or an amendment filed in response to a *Quayle* action.

   Failure to timely respond to this notice will result in:
   Abandonment of the application if the non-compliant amendment is a non-final amendment or an amendment filed in response to a *Quayle* action; or
   Non-entry of the amendment if the non-compliant amendment is a preliminary amendment or supplemental amendment.

_____ _____

Legal Instruments Examiner (LIE), if applicable Telephone No.

Advisory Action, Item 11

1. Application No. 10632725 (20040082080 A1): Claims 59-66, 68, 118-138 are pending. Claim 68 is withdrawn as drawn to a non-elected species. Claims 59-66 and 118-138 are examined.

2. The Office Action Summary, Form PTOL-326, mailed 4/26/2007, in item 4a), inadvertently omitted reference to claims 68 and 70-73 as withdrawn from consideration. However, in the Office action, mailed 4/26/2007, at p. 1, item no. 1, lines 3-4, claims 68 and 70-73 were indicated as "withdrawn as drawn to a non-elected species". Claim 68 has not been indicated as allowable and remains withdrawn from consideration. Therefore, the claims are objected to as non-compliant (see attached Notice).

Nucleotide/Amino Acid Sequence Rules

3. Applicant's provision of paper and computer disk sequence listings and statement in the Remarks after final rejection, p. 8, para 3; and amendments to the specification at p. 31, are acknowledged

Election/Restrictions

4. Claims 68 remains withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or

linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 2/9/2007.

Priority

5. This application, 10/632,725, filed 8/1/2003, claims benefit of U.S. Provisional Application Serial No. 60/461,394, filed Apr. 8, 2003, U.S. Provisional Application Serial No. 60/430,273 filed Dec. 2, 2002, and U.S. Provisional Application Serial No. 60/400,503 filed Aug. 1, 2002.

6. The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Provisional Application No.s 60/461,394, filed 4/8/2003; and 60/400,503, filed 8/1/2002, fail to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. Provisional Application No.s 60/461,394, filed 4/8/2003 and 60/400,503, filed 8/1/2002, do not provide support for methods of assaying for a pathogen in a sample, comprising antibodies. Therefore, the instant

application has an effective filing date of **12/2/2002**, which is the filing date of Provisional Application Serial No. 60/430,273.

Response to Arguments

Applicant argues that the Office action, mailed 7/21/2006, did not specify the claims that do not satisfy the requirements of 35 USC 112, first paragraph.

Applicant's arguments, entered 10/23/2006, have been fully considered but they are not persuasive. The claims currently examined do not find support in 60/461,394, filed 4/8/2003 and 60/400,503, filed 8/1/2002. These said provisional applications do not disclose or suggest assaying for a pathogen in a sample.

Information Disclosure Statements

7. The information disclosure statement (IDS), filed 6/9/2004, fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because the citation to the International Preliminary Examination Report does not provide a publication year.

Response to Arguments

Applicant argues that the IPER is not prior art. Applicant's arguments, entered 10/23/2006, have been fully considered but they are not persuasive. The IPER has been considered but the citation remains non-initialed because no publication year has been provided.

Objections to the Specification Withdrawn

8. Applicant's correction to p. 31, overcoming the objection to the specification, is acknowledged.

Withdrawn Objections/Rejections to the Claims

9. The following objections/rejections are withdrawn in view of applicant's arguments and amendments to the claims:

10. Claim 63 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 63 recites the limitation "said first fluorescent tag" in line 3. There is insufficient antecedent basis for this limitation in the claim.

Maintained Claim Rejections - 35 USC § 112, First Paragraph

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 132-137 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection is for new matter.

This rejection is necessitated by applicant's amendments to the claims.

Claims 132-137 state limitations drawn to analyzing occurring over particular ranges of seconds. These limitations do not appear to find support in the specification as filed. Applicant must point with particularity as to where these limitations are to be found in the specification as filed.

Applicant's Arguments After Final Rejection

Applicant points the drawings for providing support for the limitation of "over a period of second". The examiner respectfully submits that this is not persuasive, because the drawings do not provide support for an open-ended duration of seconds, as claimed.

13. Claims 59-66 and 118-138 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection is for lack of written description.

This rejection is necessitated by applicant's amendments to the claims.

The claims are drawn to methods of assaying for a pathogen in a sample, said method comprising: exciting said sample with radiation, said sample comprising at least

one pathogen; at least one probe, and at least one fluorescent tag; measuring the fluorescence from a subvolume of said excited sample; and analyzing the fluctuations of said fluorescence that are due to the diffusion or flow of said pathogen through said subvolume; and variations thereof.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116).

One of skill in the art cannot envision the methods comprising the genus of probes and the genus of pathogens, such that analyzing the fluctuations of fluorescence that are due to the diffusion or flow of said pathogens through a subvolume, would result in the assaying for any species of pathogen. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The antibody probes taught by the specification do not represent an representative number of species adequate to describe identifying the genus of any pathogen using the claimed method. See Fiers v. Revel, 25 USPQ2d 1601 at 1606 (CAFC 1993) and Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

The reference of Robbins and Cotran, Pathologic Basis of Disease, Second Edition, W.B. Saunders Co., Philadelphia, (1979), at pp. 22-26, teach numerous

pathogens, including biologic agents. Robbins et al., at p. 25, stress that, for example, whether an agent is a pathogen, is dependent not only upon the virulence of the agent itself, but also the susceptibility of the host. It is unpredictable that analysis of the diffusion or flow of, e.g., a bacteria through a subvolume, would allow identification of the bacteria as a pathogen. It is noted that claim 60 does not require that the specificity of the probe be specified.

One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481 at 1483. In Fiddes, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Response to Arguments after Final Rejection

Applicant argues that applicant provides working examples for the claimed invention.

Applicant's arguments, entered 6/26/2007, have been fully considered but they are not persuasive. The examiner respectfully submits that the specification does not provide a representative number of species adequate to describe the claimed genus, given that the genus of pathogens is dependent not only upon the virulence of the agent itself, but also the susceptibility of the host. It is unpredictable that analysis of the diffusion or flow of, e.g., a bacteria through a subvolume, would allow identification of the bacteria as a pathogen.

Claim Rejections - 35 USC § 112, Second Paragraph

Maintained Rejections

14. Claims 59, 118-121, 124-126, 130-132, 134 and 136 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

This rejection is reiterated for the reasons of record as set forth in the previous Office action. This rejection is necessitated by applicant's amendments to the claims.

Claim 59 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: determining the presence or absence of the pathogen.

Response to Arguments after Final Rejection

Applicant argues that the claims include all required elements or steps..

Applicant's arguments, entered 6/26/2007, have been fully considered but they are not persuasive. Claim 59 is vague and indefinite because it is unclear that the method steps are for the method as set forth in the preamble. The preamble is drawn to assaying for a pathogen. The instant rejection could be overcome by a final step drawn to "thereby assaying for a pathogen in the sample".

15. Claims 131-133 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicant's usage of the language of "identity of said pathogen is unknown" appears to read upon a mental step. It unclear as to who or what the identity of the pathogen is "unknown" or the distinguishing physical feature of a pathogen that is unknown. It is unclear as to whether the language refers to a mental step or attempts to refer to a structural limitation of the claimed product. It is not disputed that applicant may be their own lexicographer. The examiner does not argue that the term is repugnant to the usual usage in the art. Rather, it is that claim 131 does not reasonably apprise of one skill in the art as to the metes and bounds of the claimed invention.

Claims 132 and 133 recite the limitation wherein the analyzing occurs over a period of seconds, which renders the claims vague and indefinite, because the limitation is tantamount to claiming that the analyzing occurs over a period of time, and so would not apprise one of skill in the art of the metes and bounds of the claimed invention.

Response to Arguments after Final rejection

Applicant argues that identity of a pathogen might be unknown at the time of sampling.

Applicant's arguments, entered 6/26/2007, have been fully considered but they are not persuasive. The pathogen unknown at the time of sampling may be a species previously known to science. The quality of being known or unknown, is thus dependent upon the practitioner of the method; but does not affect the pathogen, itself.

As such, one of skill in the art would not be reasonably apprised of the metes and bounds of the claimed invention.

Maintained Claim Rejections - 35 USC § 102

16. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

17. Claims 59-66 and 118-125, 127, 128, 130-133, and 138 are rejected under 35 U.S.C. 102(e) as being anticipated by Rigler et al., US 6,582,903 B1.

This rejection is maintained for the reasons of record as set forth in the previous Office action. That rejection is copied below for the convenience of the reader. This rejection is necessitated by applicant's amendments to the claims.

The claims are drawn to a method of assaying for the presence of a pathogen component in a sample, said method comprising: exciting a sample with radiation, said sample comprising at least one probe capable of binding a predetermined pathogen component, and at least one fluorescent tag; measuring the fluorescence from a subvolume of said sample; analyzing the fluctuations of said fluorescence; and determining the presence or absence of said pathogen component; and variations thereof.

Rigler et al., throughout the patent, and at col. 16, line 47, teaches detecting pathogens reading on method of assaying for the presence of a pathogen component in a sample; Rigler et al., e.g., at col. 1, lines 55-58, teach fluorescence correlation spectroscopy (FCS) using chromophorous molecular structures having fluorescence properties, reading on fluorophores; wherein the fluorophorous molecules in solution are exposed to the intense exciting light of a laser, (Rigler et al. at col. 2, lines 21-24), which reads on exciting a sample with radiation, said sample comprising a complex of a target molecule to be detected and a labeled test reagent, (Rigler et al., at col. 7, lines 14-27), the receptor molecules/ligands, (Rigler et al., col. 8, lines 50-64), including antibodies, which reads further on at least one probe capable of binding a predetermined pathogen component, and at least one fluorescent tag, (Rigler et al., col. 13, lines 45-62; col. 18,

line 41-col. 19, line 2); measuring fluorescence from a volume element, reading on measuring the fluorescence from a subvolume of said sample, (see col. 12, line 62-col. 13, line 10; col. 13, line 62-col. 14, line 45); analyzing the fluctuations of said fluorescence, (Rigler et al., at col. 2, line 7-20); and determining the presence or absence of said pathogen component, (Rigler at col. 8, lines 25-30; col. 16, lines 36-47).

Rigler et al. at col. 2, line 7-31, teach that spectroscopic methods for measuring fluorescence fluctuations are employed in fluorescence correlation spectroscopy. In considering the disclosure of the instant application in regards to measuring fluctuations in fluorescence intensity in fluorescence correlation spectroscopy, the examiner respectfully notes that the instant specification states:

> Fluorescence correlation spectroscopy (FCS) is a single molecule detection method that measures the fluctuations in fluorescence intensity in a small (e.g., femtoliter) confocal volume. FCS employs a tightly focused laser beam to define the confocal volume. The diffusion of fluorescently labeled particles into and out of the illuminated volume determines the fluorescence intensity fluctuation patterns. From this data, one can extract both qualitative information and quantitative information on the molecule being studied. Such qualitative information includes, e.g., the presence or absence of molecular interaction; such quantitative information includes diffusion time, stoichiometry of the interactions, concentration of the interacting particles and the kinetics of the interaction.

Specification at pp. 1-2, bridging paragraph.

Rigler et al., at col. 12, lines-22, teach at least two differently labeled test reagents which will bind to different sequence segments of an analyte, and teach cross correlation of a chromophore 1 and a chromophore 2, (col. 13, line 45-col. 14, line 9), reading on a plurality of unique fluorescently tagged probes, as in claims 62 and 63. Rigler at col. 11, line 45-col. 12, line 22, teaches determining the crosscorrelation function and the autocorrelation function of a sample, reading on claim 64. Rigler at col. 25, lines 10-25, col. 35, lines 57-65, teach pathogens that comprise bacteria or virus, as in claims 65 and 66.

The claims are drawn to methods of assaying for a pathogen in a sample, said method comprising: exciting said sample with radiation, said sample comprising at least one pathogen; at least one probe, and at least one fluorescent tag; measuring the fluorescence from a subvolume of said excited sample; and analyzing the fluctuations of said fluorescence that are due to the diffusion or flow of said pathogen through said

subvolume; and variations thereof. These claims are anticipated by Rigler et al., for the reasons as set forth above.

Response to Arguments

Applicant argues Rigler does not disclose a method for assaying a pathogen in a sample, in a sample volume that includes one pathogen. Applicant's representative states: "A molecule is not a pathogen. A pathogen is an organism. In addition a pathogen is an agent that causes a disease state", (Reply at p. 25).

Applicant's arguments, entered 10/23/2006, have been fully considered but they are not persuasive.

Firstly, as stated in the previous Office action, claims must be given their broadest reasonable interpretation consistent with the supporting description. In re Hyatt, 211 F.3d 1367, 1372, 54 USPQ2d 1664, 1667 (Fed. Cir. 2000). The claims are drawn to pathogens. See, *e.g.*, *Invitrogen Corp v. Biocrest Mfg., L.P.*, 327 F.3d 1364, 1368, 66 USPQ2d 1631, 1634 (Fed. Cir. 1997); and MPEP 211.03. The claims and the specification do not provide a limiting definition for the term "pathogen". Dorlands's Illustrated Medical Dictionary, Twenty-fifth Edition, Saunders, Philadelphia (1979) at p. 1148, defines the term pathogen as "any disease-producing microorganism **or material**." Emphasis added. Therefore, the examiner respectfully submits that the term pathogen, when given its broadest reasonable interpretation, is taught by reference of Rigler.

The arguments of counsel cannot take the place of evidence in the record. *In re Schulze*, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965); *In re Geisler*, 116 F.3d

1465, 43 USPQ2d 1362 (Fed. Cir 1997) ("An assertion of what seems to follow from common experience is just attorney argument and not the kind of factual evidence that is required to rebut a *prima facie* case of obviousness."). MPEP 2145. Applicant's representative states: "A molecule is not a pathogen. A pathogen is an organism. In addition a pathogen is an agent that causes a disease state", (Reply at p. 25). The examiner respectfully submits that this is merely argument that is insufficient as objective evidence.

Response to Arguments after Final rejection

Applicant's arguments, entered 6/26/2007, have been fully considered but they are not persuasive. Applicant argues that a pathogen is an organism and therefore Rigler cannot teach pathogens. Rigler at col. 6, lines 46-60, disclose assaying diffusion times of viruses and cells, including bacteria. The examiner respectfully submits that the term pathogen encompasses more than an organism. Furthermore, the claims are drawn to assaying for a pathogen. Such identification is possible from components of a pathogen.

Applicant argues that Rigler does not teach analysis of diffusion or flow of a pathogen through a subvolume. The examiner respectfully submits that Rigler teaches fluorescence correlation spectroscopy (FCS) comprising measuring fluorescence from a volume element, reading on measuring the fluorescence from a subvolume of said sample, (see col. 12, line 62-col. 13, line 10; col. 13, line 62-col. 14, line 45); analyzing the fluctuations of said fluorescence, (Rigler et al., at col. 2, line 7-20); and determining the presence or absence of said pathogen component, (Rigler at col. 8, lines 25-30; col.

16, lines 36-47). Rigler, at e.g., col. 2, lines 7-20, teach FCS fluctuation analysis. Rigler at col. 2, lines 21-54, teach the use of fluorophorous molecules. Rigler teaches fluorophorous molecules, including labeled reagents such as antibodies or receptor molecules (col. 8, lines 50-64).

Rigler at col. 25, lines 10-25, col. 35, lines 57-65, teach pathogens that comprise bacteria or virus. See also, Rigler at col. 21, line 62-col 22, line 11. Rigler, e.g., at col. 11, lines 33-45, teach parallel determination of at least two different analytes in at sample, reading on a plurality of probes. The examiner respectfully submits that the term "period of seconds" encompasses time periods of less than one second.

18. Claims 59-64, 66 and 118-125, 127, 128, 130-133, and 138 are rejected under 35 U.S.C. 102(b) as being anticipated by Rigler, Journal of Biotechnology, vol. 41 (1995), pp. 177-186.

This rejection is maintained for the reasons of record as set forth in the previous Office action. That rejection is copied below for the convenience of the reader. This rejection is necessitated by applicant's amendments to the claims.

Rigler (1995), throughout the publication and abstract, and at pp. 182-184, teach methods of assaying for the presence of a pathogen component in a sample, said method comprising: exciting a sample with laser radiation, (Rigler (1995) at p. 178, Fig. 1), said sample comprising at least one probe (Rigler (1995) at p. 178, para 2) capable of binding a predetermined pathogen component, such as hepatitis B and C or HIV and

virus that is M13 bacteriophage, (Rigler (1995) at pp. 182-193, bridging paragraph, and as in claim 65) using several fluorescence labeled primers in the form of a cocktail, (also reading on claim 62), reading on methods comprising at least one fluorescent tag, and measuring the fluorescence fluctuations from an extremely small volume element, (Rigler (1995), at p. 177, para 1-2), which reads on a subvolume of said sample and analyzing the fluctuations of said fluorescence, and determining the presence or absence of said pathogen component, (Rigler (1995) at pp. 182-193, bridging paragraph).

Rigler (1995), at p. 182, Fig. 6, teaches cross-correlation in two colors, reading on a plurality of probes with different fluorophore tags, and e.g., at p. 180, teach autocorrelations, as in claims 62-64.

Response to Arguments

Applicant argues Rigler does not disclose a method for assaying a pathogen in a sample, in a sample volume that includes one pathogen. Applicant's representative states: "A molecule is not a pathogen. A pathogen is an organism. In addition a pathogen is an agent that causes a disease state", (Reply at pp. 25, 29).

Applicant's arguments, entered 10/23/2006, have been fully considered but they are not persuasive.

Firstly, claims must be given their broadest reasonable interpretation consistent with the supporting description. In re Hyatt, 211 F.3d 1367, 1372, 54 USPQ2d 1664, 1667 (Fed. Cir. 2000). The claims are drawn to pathogens. See, *e.g.*, *Invitrogen Corp v. Biocrest Mfg., L.P.*, 327 F.3d 1364, 1368, 66 USPQ2d 1631, 1634 (Fed. Cir. 1997);

and MPEP 211.03. The claims and the specification do not provide a limiting definition for the term "pathogen". Dorlands's Illustrated Medical Dictionary, Twenty-fifth Edition, Saunders, Philadelphia (1979) at p. 1148, defines the term pathogen as "any disease-producing microorganism **or material**." Emphasis added. Therefore, the examiner respectfully submits that the term pathogen, when given its broadest reasonable interpretation, is taught by reference of Rigler.

The arguments of counsel cannot take the place of evidence in the record. *In re Schulze*, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965); *In re Geisler*, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir 1997) ("An assertion of what seems to follow from common experience is just attorney argument and not the kind of factual evidence that is required to rebut a *prima facie* case of obviousness."). MPEP 2145. Applicant's representative states: "A molecule is not a pathogen. A pathogen is an organism. In addition a pathogen is an agent that causes a disease state", (Reply at p. 25). The examiner respectfully submits that this is merely argument that is insufficient as objective evidence.

Response to Arguments after Final rejection

Applicant's arguments, entered 6/26/2007, have been fully considered but they are not persuasive. Applicant argues that a pathogen is an organism and therefore Rigler (1995) cannot teach pathogens. The examiner respectfully submits that the term pathogen encompasses more than an organism; and that molecules may be considered pathogens. Furthermore, the claims are drawn to assaying for a pathogen. Such identification is possible from components of a pathogen.

Rigler (1995), at p. 178, para 3, teach fluctuation analysis in FCS. Rigler (1995), at p. 182, column 2, discloses assaying diffusion times of viruses, (p. 182).

Applicant argues that Rigler (1995) teaches away from a period of seconds. First, Rigler (1995) anticipates the claimed invention, so that an argument of teaching away is not apropos. Second, Rigler (1995), at e.g., the abstract, teaches a period of milliseconds. The examiner respectfully submits that the claimed term "period of seconds" encompasses time periods of less than one second.

Rigler (1995), at p. 182, right column, teaches use of several fluorescence labeled primers in the form of a "cocktail", thereby teaching a plurality of probes.

Applicant's arguments regarding claim 65 are persuasive, and the instant rejection of claim 65 over Rigler (1995) is withdrawn.

19. Claims 59-64, 66 and 118-125, 127, 128, 130-138 are rejected under 35 U.S.C. 102(b) as being anticipated by Weiner et al., Digestion, 2000, vol. 61, pp. 84-89.

This rejection is maintained for the reasons of record as set forth in the previous Office action. That rejection is copied below for the convenience of the reader. This rejection is necessitated by applicant's amendments to the claims.

Weiner et al., throughout the publication, abstract, and at para 1, teach measuring serum hepatitis C virus (HCV) RNA, and teach a fluorescence correlation spectroscopy method (p. 85, Methods, para 7) for assaying the pathogen, HCV in a sample, reading on assaying for the presence of a pathogen component in a sample,

said method comprising: exciting a sample with argon-ion laser, radiation, said sample comprising Cy3-labeled amplimers for HCV RNA, (Weiner et al., at p. 85, para 8), reading on a at least one probe capable of binding a predetermined pathogen component, and at least one fluorescent tag; measuring the fluorescence from a subvolume of said sample and measuring diffusion times, (p. 85, para 8), reading on analyzing the fluctuations of said fluorescence; and determining the presence or absence of said HCV.

Response to Arguments

Applicant argues Wiener does not disclose a method for assaying a pathogen in a sample, in a sample volume that includes one pathogen. Applicant's representative states: "The RNA of hepatitis C virus is not a pathogen. Therefore Weiner et al. do not teach a sample that includes a pathogen", (Reply at p 29).

Applicant's arguments, entered 10/23/2006, have been fully considered but they are not persuasive.

Firstly, claims must be given their broadest reasonable interpretation consistent with the supporting description. In re Hyatt, 211 F.3d 1367, 1372, 54 USPQ2d 1664, 1667 (Fed. Cir. 2000). The claims are drawn to pathogens. See, *e.g.*, *Invitrogen Corp v. Biocrest Mfg., L.P.*, 327 F.3d 1364, 1368, 66 USPQ2d 1631, 1634 (Fed. Cir. 1997); and MPEP 211.03. The claims and the specification do not provide a limiting definition for the term "pathogen". Dorlands's Illustrated Medical Dictionary, Twenty-fifth Edition, Saunders, Philadelphia (1979) at p. 1148, defines the term pathogen as "any disease-producing microorganism **or material**." Emphasis added. Therefore, the examiner

respectfully submits that the term pathogen, when given its broadest reasonable interpretation, is taught by reference of Weiner et al.

The arguments of counsel cannot take the place of evidence in the record. *In re Schulze*, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965); *In re Geisler*, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir 1997) ("An assertion of what seems to follow from common experience is just attorney argument and not the kind of factual evidence that is required to rebut a *prima facie* case of obviousness."). MPEP 2145. Applicant's representative states: "The RNA of hepatitis C virus is not a pathogen", (Reply at p. 29). The examiner respectfully submits that this is merely argument that is insufficient as objective evidence.

Response to Arguments after Final Rejection

Applicant's arguments, entered 6/26/2007, have been fully considered but they are not persuasive. Applicant argues that a pathogen is an organism and therefore Weiner cannot teach pathogens. The examiner respectfully submits that the term pathogen encompasses more than an organism; and that molecules may be considered pathogens. Weiner et al., throughout the publication, abstract, and at para 1, teach measuring serum hepatitis C virus (HCV) RNA, and teach a fluorescence correlation spectroscopy method (p. 85, Methods, para 7) for assaying the pathogen that is the virus hepatitis C. FCS methods inherently employ fluctuation analysis, as stated in the instant specification in the Summary of the Invention. Furthermore, the claims are drawn to assaying for a pathogen. Such identification is possible from components of a pathogen.

Applicant argues that Weiner does not teach analysis of diffusion or flow of a pathogen through a subvolume. The examiner respectfully submits that Weiner teaches fluorescence correlation spectroscopy (FCS) comprising measuring fluorescence from a volume element, reading on measuring the fluorescence from a subvolume of said sample, (see p. 85, second paragraph and last paragraph).

Weiner et al., at p. 85, last paragraph, teach analysis for 60 seconds. The examiner respectfully notes that the claims are rejected under 35 102(b) over Weiner. Weiner, at p. 88, para 6, teach the use of internal control RNAs lableled with different fluorochromes to be processed in the FCS assay for pathogen, thereby reading on a plurality of unique fluorescently tagged probes.

Applicant's arguments regarding claim 65 are persuasive, and the instant rejection of claim 65 over Weiner is withdrawn.

20. Claims 59-65 and 118-125, 127, 128, 130-138 are rejected under 35 U.S.C. 102(b) as being anticipated by Walter et al., Proc. Natl. Acad. Sci., USA, November 1996, vol. 93, pp. 12805-12810.

This rejection is maintained for the reasons of record as set forth in the previous Office action. That rejection is copied below for the convenience of the reader. This rejection is necessitated by applicant's amendments to the claims.

Walter et al., throughout the publication and abstract and at p.12805, para 1-2, teach a method of assaying for the presence of a *Mycobacterium tuberculosis* pathogen

component in a sample, said method comprising: exciting a sample with laser radiation, 9P. 12805, para 1), said sample comprising at least one primer (see Table 1, p. 12807) capable of binding a *M. tuberculosis* DNA pathogen component, and at least one fluorescent rhodamine tag; measuring the fluorescence from a investigated volume (Walter et al. at p. 12805, para 1), reading on a subvolume of said sample; analyzing the fluctuations of said fluorescence, (Walter et al. at p. 12805, para 1); and determining the presence or absence of said pathogen component.

Response to Arguments

Applicant argues Walter et al., does not disclose a method for assaying a pathogen in a sample, in a sample volume that includes one pathogen. Applicant's representative states: "A DNA is not a pathogen. Walter et al. thus fail to teach the method of claim 60", (Reply at p 31).

Applicant's arguments, entered 10/23/2006, have been fully considered but they are not persuasive.

Firstly, claims must be given their broadest reasonable interpretation consistent with the supporting description. In re Hyatt, 211 F.3d 1367, 1372, 54 USPQ2d 1664, 1667 (Fed. Cir. 2000). The claims are drawn to pathogens. See, *e.g.*, *Invitrogen Corp v. Biocrest Mfg., L.P.*, 327 F.3d 1364, 1368, 66 USPQ2d 1631, 1634 (Fed. Cir. 1997); and MPEP 211.03. The claims and the specification do not provide a limiting definition for the term "pathogen". Dorlands's Illustrated Medical Dictionary, Twenty-fifth Edition, Saunders, Philadelphia (1979) at p. 1148, defines the term pathogen as "any disease-producing microorganism **or material**." Emphasis added. Therefore, the examiner

respectfully submits that the term pathogen, when given its broadest reasonable interpretation, is taught by reference of Walter et al.

The arguments of counsel cannot take the place of evidence in the record. *In re Schulze*, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965); *In re Geisler*, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir 1997) ("An assertion of what seems to follow from common experience is just attorney argument and not the kind of factual evidence that is required to rebut a *prima facie* case of obviousness."). MPEP 2145. Applicant's representative states: "A DNA is not a pathogen", (Reply at p. 29). The examiner respectfully submits that this is merely argument that is insufficient as objective evidence.

Response to Arguments after Final Rejection

Applicant's arguments, entered 6/26/2007, have been fully considered but they are not persuasive. Applicant argues that a pathogen is an organism and therefore Walter cannot teach pathogens. The examiner respectfully submits that the term pathogen encompasses more than an organism; and that molecules may be considered pathogens. Walter et al., throughout the publication, abstract, and at para 1, teach measuring pathogen genomic sequences, particularly of Mycobacterium tuberculosis, and teach a fluorescence correlation spectroscopy method employing fluctuation autocorrelation (p. 12805) for assaying the pathogen. FCS methods inherently employ fluctuation analysis, as stated in the instant specification in the Summary of the Invention. Furthermore, the claims are drawn to assaying for a pathogen. Such identification is possible from components of a pathogen.

Applicant argues that Weiner does not teach analysis of diffusion or flow of a pathogen through a subvolume. The examiner respectfully submits that Weiner teaches fluorescence correlation spectroscopy (FCS) comprising measuring fluorescence from a volume element, reading on measuring the fluorescence from a subvolume of said sample, (see p. 85, second paragraph and last paragraph).

Walter et al., e.g., in the abstract, teach analysis for 30 seconds. Walter, at p. 12810, para 2, teaches multiplex analysis with different labeled probes, which read on a plurality of unique fluorescently-tagged probes.

Applicant's arguments regarding claim 66 are persuasive, and the instant rejection of claim 66 over Walter is withdrawn.

Claim Rejections - 35 USC § 103

21. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

22. Claims 59-66 and 118-125, 127, 128, 130-138 are rejected under 35 U.S.C. 103(a) as being unpatentable by **Kask**, US 6,515,289, in view of **Lahiri et al.**, US 2003/0138853 A1.

This rejection is maintained for the reasons of record as set forth in the previous Office action. That rejection is copied below for the convenience of the reader. This rejection is necessitated by applicant's amendments to the claims.

Kask, US 6,515,289, throughout the patent, and at col. 1, lines 5-13, teaches methods of detecting substances in a sample, said method comprising: exciting a sample with radiation, (Kask at col. 3, line 63-col. 4, line 9), said sample comprising a labeled reactant that binds to a substance, reading on at least one probe capable of binding a predetermined component, and at least one fluorescent tag (col. 8, lines 8-29); Kask at, e.g., col. 2, lines 47-63, teaches monitoring intensity fluctuations of radiation emitted by molecules in a measurement volume, reading on measuring the fluorescence from a subvolume of said sample and analyzing the fluctuations of said fluorescence; and determining the presence or absence of said component, including viruses and bacteria, (col. 6, lines 31-48; and as in claims 65 and 66).

Kask at col. 1, lines 23-teach that spectroscopic methods for measuring fluorescence fluctuations are employed in fluorescence correlation spectroscopy (FCS). In considering the disclosure of the instant application in regards to measuring fluctuations in fluorescence intensity in fluorescence correlation spectroscopy, the instant specification states:

> Fluorescence correlation spectroscopy (FCS) is a single molecule detection method that measures the fluctuations in fluorescence intensity in a small (e.g., femtoliter) confocal volume. FCS employs a tightly focused laser beam to define the confocal volume. The diffusion of fluorescently labeled particles into and out of the illuminated volume determines the fluorescence intensity fluctuation patterns. From this data, one can extract both qualitative information and quantitative information on the molecule being studied. Such qualitative information includes, e.g., the presence or absence of molecular interaction; such quantitative information includes diffusion time, stoichiometry of the interactions, concentration of the interacting particles and the kinetics of the interaction.

Specification at pp. 1-2, bridging paragraph.

Kask, at col. 8, lines 9-50, teaches a plurality of primers labeled with different dyes, reading on a plurality of unique fluorescently tagged probes, as in claims 62 and 63. Kask at, e.g., col. 5, line 65-col. 6, line 3, teach cross-correlation and auto-correlation functions, and combinations thereof, as in claim 64.

Kask et al. do not teach the detection of pathogens.

Lahiri et al., US 2003/0138853 A1, throughout the publication, and at para [0077] teach assay for the presence of a pathogen for diagnosis; and at para [0071], teaches using fluorescence correlation spectroscopy (FCS) as a detection method.

It would have been *prima facie* obvious, at the time the invention was made, for one of ordinary skill in the art to have made and used a method of assaying for the presence of a pathogen component in a sample using fluorescence fluctuation methods, such as FCS.

One of ordinary skill in the art would have been motivated to make and use a method of assaying for the presence of a pathogen component in a sample by measuring fluorescence fluctuation, because Lahiri et al. teach using FCS for detecting pathogens for diagnosis and because Kask, at col. 7, lines 37-42, teach using FCS for high throughput screening, and for diagnostic purposes, and teaches the detection of viruses and bacteria, as stated above.

One of ordinary skill in the art would have had a reasonable expectation of success in assaying for the presence of a pathogen by measuring fluorescence fluctuations because Kask et al. teach measuring bacteria and virus by such methods.

Response to Arguments

Applicant argues that a prima facie case of obviousness has not been made because the references do not describe all elements, in particular, the references do not disclose pathogens. Applicant argues that the reference of Lahiri et al. does not explain what is meant by "derived from" a body fluid. Applicant argues that the term "derived from" does not inherently mean that the sample includes a pathogen. Furthermore analytes indicative of pathogens could be, for example, antibodies to the pathogen, and not pathogens.

Applicant's arguments, entered 10/23/2006, have been fully considered but they are not persuasive.

Firstly, Lahiri et al., US 2003/0138853 A1, throughout the publication, and at para [0077] teach assay for the presence of a pathogen for diagnosis; and at para [0071], teaches using fluorescence correlation spectroscopy (FCS) as a detection method. Applicant's argument ignores the plain meaning of the reference.

Claims must be given their broadest reasonable interpretation consistent with the supporting description. In re Hyatt, 211 F.3d 1367, 1372, 54 USPQ2d 1664, 1667 (Fed. Cir. 2000). The claims are drawn to pathogens. See, *e.g.*, *Invitrogen Corp v. Biocrest Mfg., L.P.*, 327 F.3d 1364, 1368, 66 USPQ2d 1631, 1634 (Fed. Cir. 1997); and MPEP 211.03. The claims and the specification do not provide a limiting definition for the term "pathogen". Dorlands's Illustrated Medical Dictionary, Twenty-fifth Edition, Saunders, Philadelphia (1979) at p. 1148, defines the term pathogen as "any disease-producing microorganism **or material**." Emphasis added. Therefore, the examiner respectfully

submits that the term pathogen, when given its broadest reasonable interpretation, is taught by the combination of the references of Kask and Lahiri et al.

Response to Arguments after Final Rejection

Applicant's arguments, entered 6/26/2007, have been fully considered but they are not persuasive. Applicant argues that Kask fails to teach analyzing fluctuation in fluorescence of a pathogen. However, Kask teach units of a sample that can be bacteria and viruses, and claims such in dependent claim 6, 27, 49, and 72. Kask claims fluctuation analysis in claims 1, 7, 28, 45, 50, 67, 68, and 73. Thus, the examiner respectfully submits that an argument that these elements are merely items of a laundry is not persuasive.

Lahiri et al., is cited for detection of pathogens.

Kask, at least in the Brief Summary of the Invention, teach autocorrelation analysis. Kask, e.g., at col. 11, lines 19-23, provide a example of FCS analysis for rhodamine, wherein the data collection time is 60 seconds, reading on and suggesting analysis of seconds.

Thus the features of the claimed invention were known in the art at the time of claimed invention. Methods to combine, i.e., to use bacteria, as taught by Kask, that were pathogens, as taught by Lahiri, were also familiar in the prior art. The use of bacteria that were also pathogens, would be predictable, in the outcome, as there is no structural feature to distinguish a bacteria from a pathogenic bacteria. Therefore, the examiner respectfully submits that the invention would be obvious.

The examiner respectfully notes that Claim 129 is not rejected.

Conclusion

23. Claims 59-66 and 118-138 stand finally rejected. Claim 68 is objected to.

24. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark L. Shibuya, Ph.D. whose telephone number is (571) 272-0806. The examiner can normally be reached on M-F, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. J. Douglas Schultz can be reached on (571) 272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Mark L. Shibuya, Ph.D.
Primary Examiner
Art Unit 1639